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WHAT'S NEW IN INTENSIVE CARE

Sedatives in neurocritical care: the old, the new, the future

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Sedatives are among the most frequently used drugs in the intensive care unit (ICU) for a broad spectrum of indications. Maintaining light level of sedation through titration, protocolized care, sedation depth monitoring, and sedation interruptions is associated with better neurological and neurocognitive outcomes in non-brain-injured critically ill patients. In patients with brain injuries, sedatives are required for specific therapeutic purposes, such as lowering intracranial pressure (ICP), managing refractory seizures, or managing paroxysmal sympathetic hyperactivity [1]. In addition, sedation enables specific therapies often used in these patients, such as strict CO_2 control through mechanical ventilation or targeted temperature management [1].

Propofol is the most used sedative for traumatic brain injury (TBI), followed by midazolam, while the use of alpha2-agonists or barbiturates is less frequent [2]. Sedatives are usually combined with analgesics [2]. In a recent Delphi consensus paper [3], a panel of 39 international experts reached a consensus on five statements with regards to sedation, recommending: propofol and dexmedetomidine as primary sedatives; maintenance of a deep level of sedation for specific indications; to have a protocol for daily sedation holidays unless contra-indicated; to postpone these sedation holidays until after the first days in patients with an ICP monitor; and to use clinical scales such as the Richmond Agitation Sedation Scale (RASS) to monitor depth of sedation. There was no consensus on the use of midazolam as primary agent or the use of ketamine or opioids as adjuvants; the maintenance of a light level of sedation in neuro-ICU patients; and the use of electro-encephalography (EEG)-based monitors. While experts agree that depth of sedation monitoring using processed EEG (pEEG) is accurate in general ICU patients who are deeply sedated or when clinical evaluation is not possible [4], it is unclear what their value would be in brain-injured patients. Automated pupillometry has also been proposed to monitor depth of sedation [5] but brain stem lesions or intracranial hypertension might confound its use in the setting of brain injury [6]. Scheduled sedation interruptions have a limited yield when it comes to revealing relevant clinical findings, while there are important concerns regarding safety [7]. The SIBICC group could not find consensus on relative and absolute contraindications of sedation-stopping rules and decided to construct heatmaps representing the most relevant decision variables under differing intracranial hypertension scenarios [8].

It is crucial to understand the potential neuroprotective and neurotoxic properties of sedatives (Figure 1), even while caution is warranted when extrapolating findings from preclinical studies. Evidence on the outcome benefit of specific agents or combinations of sedatives is lacking. Propofol decreases CBF, CMR, and ICP in a dose-dependent way [1], but is a negative inotrope and systemic vasodilator which can compromise cerebral perfusion pressure (CPP). Prolonged high-dose infusion is associated with the rare but often fatal propofol infusion syndrome. Propofol can act as an antioxidant in preclinical brain injury models of ischemia/reperfusion and TBI and may have anti-inflammatory and anti-apoptotic effects, while it can both inhibit and promote autophagia in the hippocampus [9]. **Midazolam** also reduces CBF, CMR, and ICP (albeit less than propofol) with less impact on hemodynamics [1]. In addition to its anti-seizure activity, midazolam exhibits neuroprotection by acting on neurodegeneration and neuroinflammation

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[9]. However, in adult [10] and pediatric [11] critically ill patients, prolonged use of midazolam is associated with worse long-term neurocognitive outcomes, a major reason for concern. Moreover, the unfavorable pharmacokinetic profile of midazolam, especially when administered in prolonged continuous infusions, will interfere with the neurological exam and neuroprognostication. **Remimazolam**, a novel ultra-short-acting benzodiazepine, is metabolized by tissue-esterases and does not accumulate, which is promising in this setting but needs further studies [12].

Inhaled anesthetics only have a limited application in the neuro-ICU because of their cerebrovascular effects and will not be discussed here.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, was previously banned in brain injury because of concerns of intracranial hypertension, which do not appear to be justified [13]. Whether a causal association between the prolonged use of ketamine and cholestasis exists remains a subject of debate [14]. Cortical spreading depolarizations (CSDs) are waves of disrupted electrical activity that propagate slowly across the cortex, associated with ionic imbalances in the grey matter of ischemic or injured brain tissue. In contrast to other (GABA-acting) sedatives, ketamine is the only agent known to attenuate or stop CSDs, highlighting its potential as a neuroprotective agent [15]. Three randomized controlled trials (RCTs) are currently investigating its use in the neuro-ICU: Ketamine Neurologic Deficit trial (KIND, NCT02636218), Ketamine for Thrombolysis in Acute Ischemic Stroke trial (KETA, NCT02258204) and Brain injury and Ketamine trial (BIKe, NCT05097261).

The alpha2-agonist **dexmedetomidine** has only minimal effects on CBF, CMR, and ICP [1], although bradycardia and hypotension may lower CPP. In different types of brain injury, dexmedetomidine could be neuroprotective by reducing catecholamine levels and modulating glutamate release, metabolism, and synaptic clearance. Potentially, neuroprotective effects are mediated through modulation of key signaling pathways, including TLR4/

NF-κB, Nrf2/ROS, and PI3K/Akt/mTOR, limiting secondary neuronal injury and promoting neurovascular stability [16].

Future directions

The low-level scientific evidence for using sedatives in neurocritical care setting contrasts with their widespread use. Because of their targeted indications in brain-injured patients, RCTs are challenging in this field, as sedatives cannot always be avoided or withdrawn without major consequences. Important research questions remain, including but not limited to: (1) the optimal choice of sedative or sedative combination for different indications in neurocritical care, and how to escalate; (2) for TBI specifically, integration of these findings in the existing tiered guidelines; (3) the choice of sedative target and the value of sedative depth monitoring targets using EEG, pEEG, pupillometry, or other techniques, especially in deeply sedated patients; (4) the development of safe evidence-based de-escalation or wake-up strategies; (5) confirmation studies on the neuroprotective effects of different compounds, in particular for GABA-acting agents, ketamine, and alpha2-agonists; (6) safety studies on their eventual neurotoxic effects. To advance in this fascinating field, high-quality research is urgently needed to refine sedation practice and enhance patient outcomes.

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Most frequently used sedatives in Neurocritical Care.

NEUROTOXIC

PROPOFOL

- Negative inotrope + vasodilator: CPP ↓
- PRIS
- Autophagia ↑

MIDAZOLAM

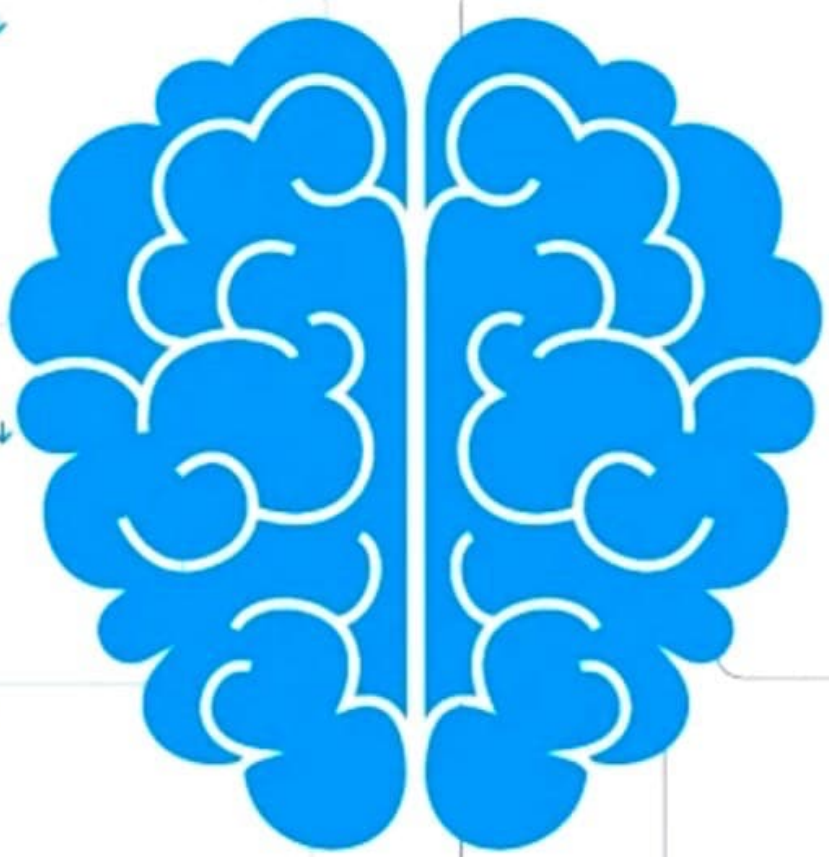
- Long-term neurocognitive outcome ↓
- Accumulation: Neurological exam ↓
  Neuroprognostication ↓

DEXMEDETOMIDINE

- Bradycardia and hypotension: CPP ↓

KETAMINE

- Cholestasis ?



NEUROPROTECTIVE

PROPOFOL

- CBF ↓↓
- CMR ↓↓
- ICP ↓↓
- Antioxidant
- Anti-inflammatory
- Anti-apoptotic
- Autophagia ↓

MIDAZOLAM

- CBF ↓
- CMR ↓
- ICP ↓
- Inhibition seizures
- Neurodegeneration ↓
- Neuroinflammation ↓

DEXMEDETOMIDINE

- Catecholamine levels ↓
- Modulating glutamate release and metabolism
- Secondary neuronal injury ↓
- Neurovascular stability ↑

KETAMINE

- CSDs ↓
- Reduced excitotoxicity

REMIMAZOLAM

- No accumulation